PART ONE

ANATOMY AND PHYSIOLOGY OF THE CEREBELLAR SYSTEM

ONE

Introduction

1.1. History

In the introductory chapter of his magnificent three-volume monograph, *The Comparative Anatomy and Histology of the Cerebellum*, Olof Larsell (1967; Larsell and Jansen, 1972) provides a history of the cerebellum in its gross aspects, which reads in part as follows (additional historical details can be found in Clarke and O'Malley 1968):

> Herophilus (335–280 B.C.) is usually credited with recognition of the human cerebellum as a distinct division of the brain. Aristotle (384–322 B.C.), however, calls it parencephalis, indicating that he did not regard it as part of the principal mass of the brain. The great Galen (A.D. 131–200) designated the vermis cerebelli "the worm-like outgrowth" (epiphysis scolexoides). The arbor vitae [the treelike set of outlines of white substance seen on a median section of the cerebellum] was described by Thomas Willis (1664) in his *Cerebri Anatome* as "ramificatio cerebelli ad foramen arboris." The latter author also suggested that the cerebellum presides over the involuntary movement of the body, whereas the cerebrum controls those movements brought about by volition. The first good drawing of the vermis was publishes by Heister (1717), but Vesalius (1543) had already included in his *Fabrica* rather crude illustrations of the entire cerebellum which are in striking contrast to his beautiful figures of muscles, bones, and other structures. Haller (1777) described the cerebellar hemispheres under the name lobi, and Malacarne (1780) gave a detailed description of the entire organ. Many of the terms which Malacarne introduced are still in use. He also described the surface folia or "laminette," giving their total number as 500 to 780. In the cerebellum of an idiot, he found only 340 folia, leading him to conclude that intelligence depends on the number of cerebellar folds. . . .
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> The earlier studies of the cerebellum in animals were largely experimental in execution. Rolando (1809) removed the cerebellum in fishes, reptiles, and mammals, described the disturbances of voluntary movements that resulted, and

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pointed out that cerebellar ablation does not affect sensation. Flourens (1844) confirmed and extended Rolando's observations, emphasizing the exaggeration of tendon and antigravity reflexes and the curious stiff-legged locomotion, with retraction of the head that followed ablation of the cerebellum in birds. [Purkinje's original description of the pear-shaped cell somata was made in Prague in 1837; see also Brazier 1988]. Ferrier (1876) reported his observations on the responses of the eyes, head, and neck to electrical stimulation of the cerebellum in dogs. Luciani (1891) described the results in the dog of complete removal of the organ, and Sherrington (1900) defined the cerebellum as the "head ganglion of the proprioceptive system," holding that it functions as a whole because it deals with the musculature of the body as a whole rather than with individual muscles. This concept was the dominating influence in cerebellar physiology for more than forty years.

During the last decade of the nineteenth century a new approach toward an understanding of the organ was begun by studies on its comparative anatomy and its embryonic development. The first article to appear in the *Journal of Comparative Neurology* was a comparative paper on the cerebellum by C. L. Herrick (1891).

There have been many attempts in the past to characterize the essential function of the cerebellum, of which the one by C. J. Herrick (1924b; the two Herricks were brothers) can serve as an example:

The cerebellum is primarily the balancing brain, controlling posture, regulating and coordinating all movements of precision of the skeletal musculature, and maintaining muscular tone. Its stabilizing influence may be compared with the action of a gyroscope on a large steamship, ensuring the steady progress of the vessel in its course by compensating the buffeting of wind and waves. The role of the cerebellum is that of proprioceptive adjustor.

According to Dow and Moruzzi (1958 p. 4), it was Flourens (1824, 1842) who introduced the concept of the function of the cerebellum as coordinating movements. Thus, after cerebellar ablation, the possibility of executing movements remained, but the coordination of these movements was lost.

1.2. The Cerebellum at Present

Ito (1984) published a magnificent, comprehensive, treatment of the cerebellum, which was preceded by that of Eccles, Ito, and Szentágothai (1967), and before that, by the book of Dow and Moruzzi (1958). Subsequently, a vast additional literature on the cerebellum has emerged and continues to appear, seemingly at an ever-increasing rate. For example, eight full papers, 43 open peer commentaries, and the responses to the latter by the authors of the full papers, under the general topic, "Controversies in neuroscience IV: Motor learning and synaptic plasticity in the cerebellum" (Bell, Cordo, and Harnad 1996), are included in the September 1966 issue of *Behavioral and Brain Sciences* (Vol. 19, No. 3). Two issues of *Learning and Memory* (Vol. 3, No. 6, and Vol. 4, No. 1) were devoted to the cerebellum as were paired issues of

Trends in Neurosciences (Vol. 21, No. 9, Sept. 1998), and *Trends in Cognitive Sciences* (Vol. 2, No. 9, Sept. 1998). In an interesting short autobiographical note, Ito (1999) briefly traced the history of the discovery of the inhibitory action of the cerebellum, the evolution of the concept of synaptic plasticity, and its demonstration experimentally.

1.3. The Perspective of This Book

The present work, the focus of which is the question of the cerebellum as an adaptive controller, has a relatively narrow perspective. Correspondingly, in the background to this main theme, only the most directly relevant aspects are considered, for the most part. In no way is a comprehensive treatment of the cerebellum intended or attempted. Some repetition can be found; this is partly intentional, to emphasize important points, and partly unintentional.

In Part I (Anatomy and Physiology of the Cerebellar System – a term used here to include the cerebellum itself, its nuclei, and the inferior olive), a brief treatment of the evolutionary or comparative anatomical aspects (Chapter 2) of the cerebellum is given. In the chapter on anatomy and physiology of the cerebellar cortex itself (Chapter 3), somewhat greater emphasis is placed on the former than on the latter. In subsequent chapters, emphasis is placed on those connections and components of the cerebellar system that appear to be of particular importance in relation to the question of cerebellar mechanisms (e.g., the mossy fibers; Chapter 4), the inferior olive and associated climbing fibers (e.g., the mossy fiber and climbing fibers constituting the major input systems to the cerebellar cortex; Chapter 5), the cerebellar nuclei (Chapter 6), which together with the vestibular nuclei constitute the output system of the cerebellar cortex, and the nucleocortical and nucleo-olivary pathways (Chapter 6).

In Part II (Cerebellar Functions), limited aspects of cerebellar mechanisms are discussed, including synaptic plasticity (Chapter 7) as a specific mechanism of cerebellar adaptability (adaptive control), the vestibulocerebellum (Chapter 8) as the simplest form of cerebellar function, cognition and imaging studies (Chapter 9), and conditioning and timing (Chapter 10). To include human disease in the survey of actual or presumed cerebellar function, aspects of cerebellar pathology and pathophysiology and their clinical manifestation are included (Chapter 11). Specialized cerebellar-like structures in certain fish (i.e., the valvula and the electroreceptive lateral lobe and the mammalian dorsal cochlear nucleus), which are found in these animal groups in addition to a true cerebellum, are included (Chapter 12) because of their resemblance in certain respects to the cerebellum itself, even if the functions of these organs and their relationship to the cerebellum remains unclear in part.

In Part III (Models and Theories), as background to the consideration of adaptive control models of the cerebellum, a relatively limited survey of a number of nonadaptive theories and models (the two terms are used more or less interchangeably) of cerebellar function are discussed (Chapter 13). A review of the closely related topics of adaptive control and neural nets (Chapter 14) follows. Several specific features of adaptive controllers are next illustrated in an adaptive controller (adaptive signal

processor) of the author's own design and construction (Chapter 15). A survey of several adaptive control models of the cerebellum then follows (Chapter 16).

In Part IV (Summary and Conclusions), a selective recapitulation of material in earlier chapters is presented, together with a detailed comparison between an adaptive signal processor and the vestibulo-ocular reflex as an example of the operation of the cerebellar system (Chapter 17). Some remaining questions are also discussed. In sum, the marshalled evidence that the cerebellum can be considered at least in part as an adaptive controller appears to be very strong. At the same time, however, the cerebellar system itself appears to lack the capability of true prediction, for which a specific time mechanism would be required. The site of the latter capability, perhaps distributed in location, remains unclear.

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Comparative Anatomy of the Cerebellum

> If we can discover what functional factors were primitively concerned in the initial
> differentiation of the cerebellum from preexisting bulbar structures and some of
> the steps by which additional functional systems of diverse kinds were drawn into
> the cerebellar complex, some light may be shed on the great problems of the
> analysis of higher cerebellar functions.   (C. J. Herrick 1924b)

It is from the standpoint that a brief survey of the circumstances under which the
cerebellum and its Purkinje cells developed in phylogeny could shed some light on
the evolution of its organization and functions in higher forms that this review, mostly
from classical sources, is presented. This survey is based primarily on the following
sources: Ariëns Kappers, Huber, and Crosby (1960), Crosby (1969), Herrick (1924a,
1924b), Larsell (1967), Larsell and Jansen (1972), Llinás (1969), Llinás and Hillman
(1969), Nieuwenhuys (1967), Schnitzlein and Faucette (1969), Butler and Hodos
(1996), and Nieuwenhuys, ten Donkelaar, and Nicholson (1998). Some additional
aspects of comparative anatomy of the cerebellum are included in Chapter 12, which
discusses cerebellar-like structures in certain fish, including the valvula of mormyrid
fish, the electrosensory lobe, and the mammalian dorsal cochlear nucleus.

2.1. Origins of the Cerebellum

Larsell (1967; pp. 6–7) summarized the early phylogeny of the cerebellum as follows:

> The primitive predominantly vestibular and lateral-line organ cerebellum of the
> lampreys [eel-like fish with a round mouth] is continued in the sluggish urodeles
> [tailed amphibians] and higher forms as a laterally situated vestibular and lateral-
> line subdivision, medial to which develops a corpus cerebelli whose fiber tract
> connections are quite different. The corpus cerebelli receives proprioceptive and
> other sensory impulses and becomes the predominant feature of the cerebellum

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in the vertebrates above the sluggish urodeles, as well as in the active types of
fishes such as selachians [sharks, skates, and rays] and teleosts [bony fish].

Microscopically, it is evident that precursors of Purkinje cells arose amid granule
cells, first irregularly in location and then in a progressively layered fashion: the layer
of Purkinje cells. The Purkinje cells themselves progressively developed extensive
dendritic trees that increasingly become confined to a single plane, through which
the parallel fibers (the axons of granule cells) thread, initially in a somewhat random
fashion but increasingly at right angles, not unlike the wires strung on the cross-arms
of telephone poles of former times.

In a departure from the main trend of cerebellar evolution, the valvula (Chapter
12) develops in association with the lateral line organs and electrosensory system of
certain fish, becoming large enough to cover the rest of the brain. In the detailed
anatomy of this unusual structure, the molecular layer (constituted of the parallel
fibers and apical dendritic tree of the Purkinje cells), as well as the layer of Purkinje
cells themselves, becomes greatly folded or foliated. The granular layer of granule
cells, however, does not participate in this folding, nor do its axons bifurcate; the par-
allel fibers arise directly from the granule cells. This arrangement must be of special
significance in relation to the processing of data from lateral line organs and elec-
troreceptors, perhaps in the capacity of phased arrays for beam forming (Chapter 12).

The origin of the cerebellum in close association with nuclei of the eighth (vestibu-
lar) nerve and the lateral line nerves perhaps suggests that this part of the cerebellum
originated as a means of carrying out some type of transformation of the coordinate
system of input data from the vestibular organ and the lateral line organs. Bullock
(1969) suggested that the function of the cerebellum might be along the lines of an
organ primarily computing and representing, in some analogue fashion, an image of
the relations of the body in space. In this connection, it is relevant to note that, in the
counterpart of the vestibular system among manmade navigation systems (i.e., the
so-called strap-down or vehicle-oriented inertial navigation systems), such a trans-
formation of coordinates must be carried out by a central computer on the basis
of the input data from the motion sensors (angular, rectilinear; Barlow 1964, 1966;
Siouris 1993; see also Chapter 12). It should be noted that this part of the cerebellum
in lower forms, and its counterpart in higher forms (as the flocculonodular lobe),
is slightly different in its histology from the main body of the cerebellum (corpus
cerebelli). Thus, Brodal (1967) pointed out that the mossy fibers in the flocculus and
nodulus (and also the caudal part of the uvula and the dorsal paraflocculus) of the cat,
vestibular fibers terminate with more profuse branching and a greater number and
density of terminal globules than is the case with the "classical" (nonvestibular) type
of mossy fibers. A relatively greater number of Golgi cells appeared to be associated
with these "vestibular" mossy fibers.

2.2. Fish

In vertebrates, the cerebellum develops from two bilaterally symmetrical formations
located dorsally at the upper end of the medulla oblongata (the rhombencephalon),
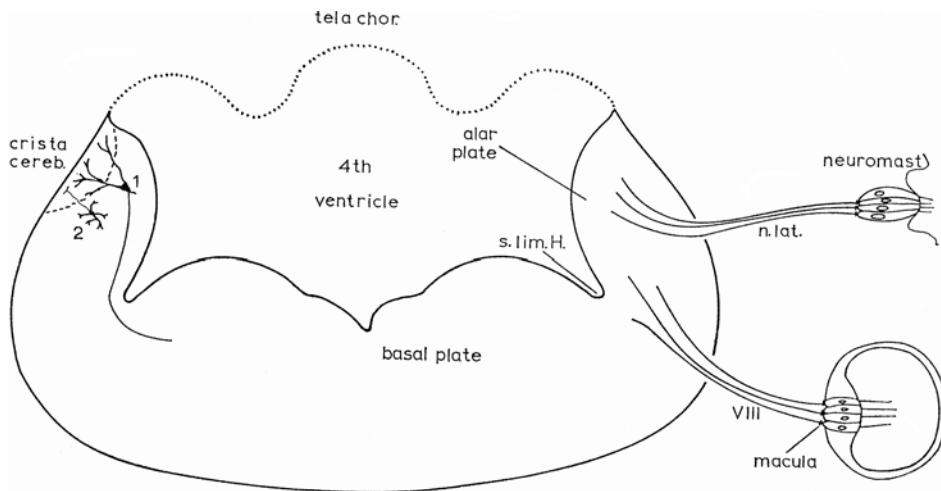
Figure 2.1. Diagrammatic transverse section through the upper medulla oblongata of a lamprey, showing (on the right) the similarities between receptor cells of the lateral line nerve and the vestibular nerve, and (on the left) the crista cerebellum or prototype cerebellum with a precursor Purkinje cell (1) and granule cell (2). crista cereb., crista cerebellaris; n. lat., nervus lateralis; tela chor., tela choroidea; s. lim. H., sulcus limitans of His. (From Nieuwenhuys 1967; reprinted by permission of the author.)

in the region of termination (in their respective nuclear complexes) of the fibers from the eighth or vestibular nerve and the lateral line nerves. This area is sometimes termed the area octavolateralis. Thus, the oldest afferent paths to the cerebellum are those of the vestibular and, in fish (and also in amphibia), of the lateral line systems. This area is also the area of termination of the trigeminal nerve. This arrangement is illustrated in Figure 2.1 for the lamprey (a member of the cyclostomes, that is, eel-like fish having a round suctorial mouth and having a brain length of 1 centimeter). The lamprey is the lowest form in which there is a clearly distinguishable cerebellum. Whether still lower forms of vertebrates possess a cerebellum (e.g., the myxinoids, the most primitive living vertebrates) has been an issue of much debate (Nieuwenhuys 1967).

In bony fish (teleosts), it has been proposed that the cerebellar auricles, which receive a large input from the vestibulolateral line system, constitute the vestibulocerebellum and are the homologues of the flocculonodular lobe of higher vertebrates, whereas the corpus cerebelli, receiving spinocerebellar and tectocerebellar fibers, is the homologue of the vermis of higher vertebrates (Ariëns et al. 1960).

It is relevant to note that the labyrinth (the three semicircular canals together with the saccule and utricle) and the lateral line organs of lampreys (*Petromyzontidae*) have a remarkable structural, as well as functional similarity, which is evident from the right side of Figure 2.1. An important difference between the two structures is that the arrangement of the lateral line organs is such that they are sensitive to relative motion of the fluid surrounding the animal, whereas the labyrinths, having basically the same sensing mechanism, are sensitive to fluid, the endolymph, which is trapped in the labyrinths. Thus, by means of detection of the motion of fluid, the

lateral line organs detect the occurrence of external currents, principally to detect
and locate other moving animals, whereas the labyrinth serves to provide information
concerning the animals' own equilibrium of the body and orientation in space (i.e.,
concerning gravity and inertia).

It is evident that these two types of information, which can be considered pro-
prioceptive and exteroceptive, respectively, are complimentary, a point that will be
relevant to a consideration (following) of the question of function of the primitive
cerebellum. It should be noted that another part of this primitive cerebellum receives
additional inputs (e.g., tectocerebellar and spinocerebellar; Nieuwenhuys 1967).

In adult lampreys, the vestibulolateral lobe receives input from the vestibular
apparatus and the lateral line organs, whereas the corpus cerebelli (cerebellar body)
receives spinal, bulbar, and trigeminal fibers. This major division of the cerebellum
into two parts is continued in higher forms. In fishes and amphibia, precursors of the
cerebellar nuclei can be recognized.

Histologically, the area of the brain of lampreys in which the two nerves (vestibular
and lateral line) terminate consists principally of small granular cells that have a few
short dendrites and a laterally directed axon that bifurcates longitudinally (Fig. 2.1,
left side, 2). These bifurcated axons are the forerunners of the parallel fibers. Scattered
among the granular cells are larger neurons having long dendrites extending in the
same direction as the axons of the granule cells (Fig. 2.1, left side, 1), with axons that
may curve downward and medially. These are the precursors of the Purkinje cells.
The neuropil zone of intermixing of the axons of the granular cells and the dendrites
of the larger cells is termed the crista cerebellaris or cerebellar crest, also known
as the molecular layer. The two intermingled cell types form a cell layer. The small
granule cells are equivalent to those in higher forms, and change little in phylogeny.
The larger cells have been considered, as just mentioned, to be the precursors of
Purkinje cells. It should be noted, however, that true Purkinje cells are characterized,
among other features, by the fact that their dendrites branch in a single plane, whereas
the dendritic tree of the larger cerebellar cellular elements is not confined to one plane
(Nieuwenhuys 1967).

The cerebellum of cartilaginous fish (sharks and rays) is considerably larger than,
and much further differentiated than, that of the round-mouth fish (cyclostomes),
and the larger ones display grooves in the cerebellum, the number of which increases
with the size of the body. It is also in this group of fishes that the Purkinje cells
spread their dendrites, which are covered with numerous spines, in a single plane. Of
particular note is the fact that the cartilagenous fishes have an olivocerebellar system,
which accompanies the caudal portion of the spinocerebellar tract toward the body
of the cerebellum (corpus cerebelli). The olivocerebellar fibers originate from the
contralateral inferior olive and terminate in all parts of the body of the cerebellum.

2.3. Amphibia and Birds

In comparison with the salamander (Urodela, or tailed species), frogs (Anura, or
tailless species) show a much more massive and more highly differentiated devel-
opment of the cerebellum. This applies particularly to the Purkinje cells, which now
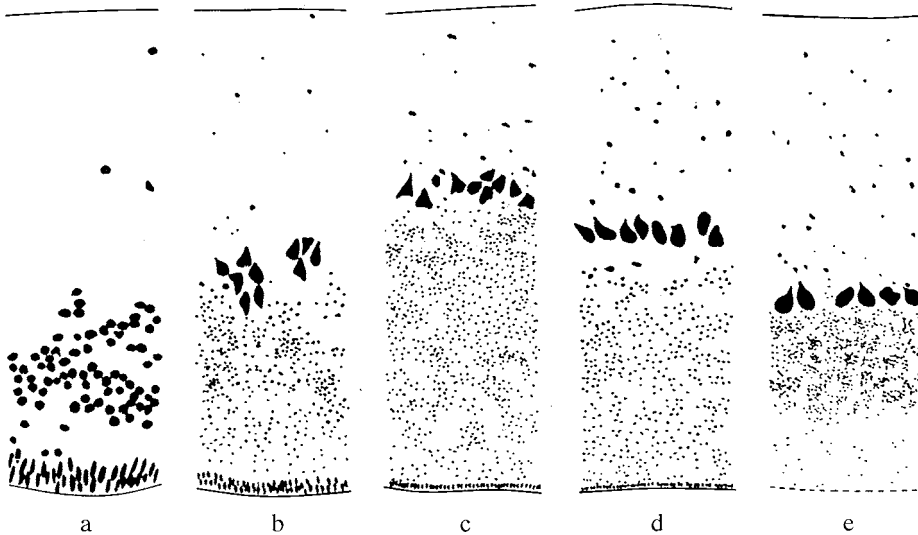
Figure 2.2. Sections showing the cell picture of the cerebellum of some representative vertebrates: (a) lamprey, (b) lungfish, (c) turtle, (d) lizard, and (e) pigeon. Note the progressive trend toward strict layering of the Purkinje cells from (b) to (e), and the diminution of size of granule cells after (a). (From Nieuwenhuys 1967; reprinted by permission of the author.)

constitute a distinct zone between the granular and the molecular layers (see Fig. 2.2 for the general trend toward layering). Further, the dendrites of the Purkinje cells are clearly oriented in a sagittal plane and show a more complex ramification (see Fig. 2.3 for the general trend). In crocodiles, the cerebellar cortical afferent and efferent
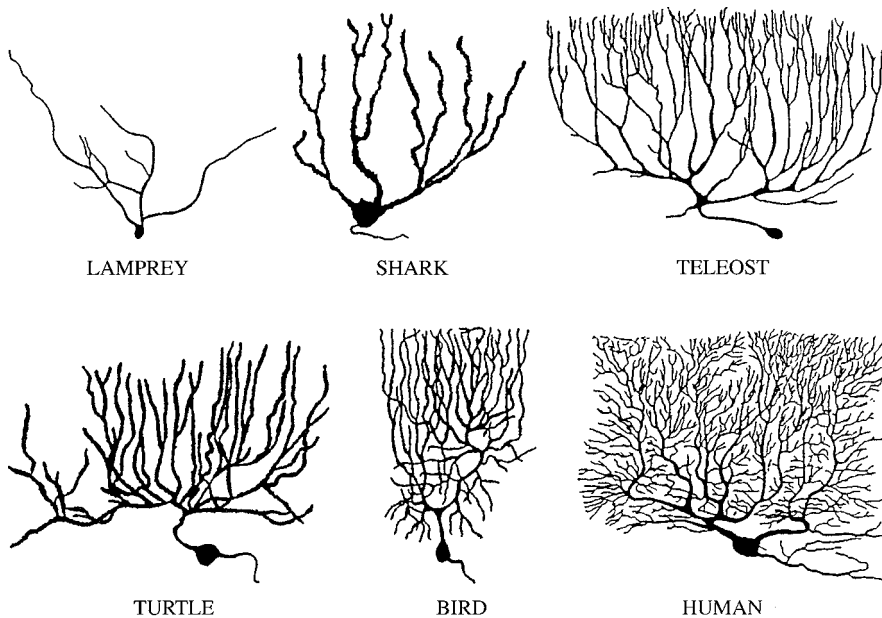

Figure 2.3. The progressive elaboration of Purkinje cell dendritic tree from lower vertebrates to humans. (From Nieuwenhuys 1967; reprinted by permission of the author.)